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ORIGINAL RESEARCH ARTICLE

Tolerability and Reactogenicity Profile of mRNA SARS-Cov-2 Vaccines from a Mass Vaccination Campaign in a Tertiary Hospital: Between-Vaccine and Between-Population Prospective Observational Study (VigilVacCOVID Study)

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Abstract

Background The comparative safety profile of SARS-Cov2 vaccines requires further characterization in real-world settings.

Objectives The aim of the VigilVacCOVID study was to assess the short-term safety of BNT162b2 and mRNA-1273 during the vaccination campaign of healthcare professionals (HCPs) and solid-organ transplant recipients (SOTRs) at a hospital clinic.

Methods We conducted an observational, prospective, single-center, post-authorization study to characterize short-term adverse reactions (ARs) after vaccination. The primary endpoint was to assess between-vaccine differences (HCPs receiving BNT162b2 or mRNA-1273) and between-population differences (HCPs and SOTRs, both receiving mRNA-1273) in the risk of any ARs. Propensity score and covariate-adjusted multivariate models were used. The key secondary endpoint was to provide a descriptive assessment of the frequencies and intensity distribution of ARs.

Results We included 5088 HCPs and 1289 patients. mRNA-1273 showed greater reactogenicity than BNT162b2, with an odds ratio (OR) for any AR of 3.04 (95% confidence interval (CI) 2.48–3.73; p value: < 0.001) and a higher frequency and intensity of reported ARs. Compared with HCPs vaccinated with mRNA-1273, SOTRs showed a lower risk of ARs (OR = 0.36; 95% CI 0.25–0.50), with fewer and less severe ARs. Age, sex, and previous SARS-CoV-2 infection were statistically significant covariates for the risk of any AR. A history of drug allergy was significant in the comparison between vaccines (BNT162b2 vs. mRNA-1273), but not in that between SOTRs and HCPs.

Conclusions Our study shows that mRNA-1273 had greater reactogenicity than BNT162b2. Overall, both vaccines had an adequate tolerability profile. mRNA-1273 vaccination caused fewer ARs with milder severity in SOTRs.

1 Introduction

The short-term safety of SARS-Cov-2 mRNA vaccines is reasonably well characterized from clinical trial data [1, 2] and pharmacovigilance sources [3–6]. Real-world studies have been published beyond the controlled context of clinical trials [7–12]. It is important to continue to provide additional supporting evidence on the safety profile of SARS-CoV-2 vaccines, especially at a time characterized by severe distress and anxiety caused by the pandemic and the initial uncertainties surrounding vaccination. Millions of SARS-CoV-2 vaccine doses have been administered worldwide, with serious adverse reactions (ARs) being rare or very rare. However, it is important to continue collecting safety information on real-world scenarios to further elucidate aspects deserving evaluation. One aspect that needs to be addressed in real-world studies is the comparative tolerability and safety profile of the vaccines, such as BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna), in clinical practice. Another aspect is the direct comparison of the reactogenicity and tolerability profile of vaccination in immunocompromised patients. It is known from experience with other vaccines that solid-organ transplant recipients (SOTRs)

The members of The VigilVacCOVID Group are listed in Acknowledgements.

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Key Points

Further vaccine safety data from large real-world cohorts are needed.

Our study provides data from a systematic, prospective comparison, showing higher reactogenicity of mRNA-1273 but an overall adequate tolerability profile of both SARS-CoV-2 vaccines, supporting existing evidence.

Our data show a lower reactogenicity in solid-organ transplant recipients (SOTRs), as expected. The impact of covariates such as age or previous SARS-CoV-2 infection suggest a potential role of immunogenicity in differences in the safety profile between SOTRs and healthcare professionals. These data provide additional supporting evidence for medical practice, given the proven efficiency of vaccination for public health and the increasing need for reassuring messages about the safety of SARS-CoV-2 vaccines.

present less robust immune responses than nontransplant patients [13]. Studies have found a reduced humoral immune response to BNT162b2 and mRNA-1273 mRNA vaccines in SOTRs after the first and second doses, measured by antispike antibody responses [14, 15] in kidney [16], lung [17], heart [18, 19], liver [20], and in general in SOTRs [15], who are underrepresented in clinical trials. However, many immunosuppressed patients and patients with other comorbidities have already been vaccinated with up to four doses in many countries, and few prospective studies have been specifically designed to target these patients. So far, no specific safety signals have been detected in these patients. However, further prospective real-world data are required to strengthen this reassuring message on vaccination and provide additional evidence on how the reactogenicity profile is elicited, especially in immunocompromised populations compared with healthy vaccinated persons.

The main aim of the VigilVacCovid-HCP Project was to capture a complete short-term safety profile of the incidence of ARs, comparing two mRNA vaccines, BNT162b2 and mRNA-1273, in terms of the incidence and severity of ARs. In addition, the study aimed to compare two populations of participants vaccinated with mRNA-1273 (healthcare professionals (HCPs) and SOTRs), in terms of the incidence and severity of ARs.

2 Methods

An active surveillance program was developed by the Pharmacovigilance Technical Committee (PhVTC) of the Hospital Clinic of Barcelona. The PhVTC is a multidisciplinary group with representatives from Clinical Pharmacology, Allergology, Pharmacy, Dermatology, Preventive Medicine, Immunology, Hospital Quality Management, and Nursing Professionals. Under the mandate of the PhVTC, the Department of Clinical Pharmacology, with the close collaboration of the Departments of Preventive Medicine and Epidemiology and the Department of Occupational Health Care, designed and implemented an active surveillance program with specific procedures for vaccine safety monitoring and integrated care processes for adverse event clinical management and reporting to the regulatory authorities. Vaccinated persons were informed of the program with a leaflet describing the objectives and methods before vaccination at the vaccination center. The information was explained again when calls were made after each dose. The survey was only delivered if the person agreed. The whole procedure was explained in the protocols assessed and approved by the Research Ethics Committee of the Hospital Clinic (references: HCB/2021/0684 and HCB/2021/0685).

The active surveillance program was designed as a prospective, observational, single-center post-authorization study aimed at characterizing short-term ARs after vaccination. The study was reported following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for cross-sectional studies [21] (see eTable 15 the Electronic Supplementary Material (ESM)).

2.1 Vaccination Campaign

The vaccination campaign began in the Hospital Clinic of Barcelona, a tertiary care Hospital, on 7 January 2021. The first group to be vaccinated were HCPs. SOTR patients started vaccination on 2 March 2021. The type of vaccine administered was determined by local authority guidance and availability depending on the national supply. Initially, BNT162b2 was the only vaccine available for HCPs. The vaccination plan for HCPs was amended on 22 January with the inclusion of mRNA-1273. Vaccination of SOTRs began on 1 March with mRNA-1273. Two doses were the usual vaccine dose at the time the study was conducted. As of May 2022, three doses in the general population and four doses in immunocompromised patients are recommended by the Spanish Ministry of Health [22].

2.2 Active Surveillance Program

The surveillance program was substantiated by a previously agreed pharmacovigilance plan that aimed to cover all vaccinated staff of the hospital and affiliated institutions (Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS) and Fundació Clinic per a la Recerca Biomèdica (FCRB)) and SOTR patients from 7 January until 30 April 2021. The primary objective was to make a comparative

descriptive assessment of the safety profile and reactogenicity of the two vaccines.

A structured questionnaire was designed containing demographic and medical data and ARs occurring after each vaccine dose.

A predefined list of ARs was agreed on based on the safety profile described in the Summary of Product Characteristics (SmPC) and the European Public Assessment Report (EPAR) of each vaccine [23–26] (see ESM eTable 13). These were considered solicited ARs. In addition, some ARs of special interest from the list of the ACCESS [3] and SPEAC Projects [5] and the Brighton Collaboration criteria were included in the predefined list of solicited ARs [27]. The following solicited ARs were included (as per Preferred Term (PT) level of the version 24.0 of the Medical Dictionary for Regulatory Activities (MedDRA): Injection site pain (PT: Injection site pain); arm pain (PT: pain in extremity); fatigue, asthenia (PT: fatigue); headache (PT: headache); fever (PT: pyrexia); muscle pain (PT: myalgia); malaise (PT: malaise); joint pain (PT: arthralgia); injection site swelling (PT: application site swelling); injection site redness (PT: application site redness); shoulder pain (PT: musculoskeletal pain); injection site pruritus (PT: vaccination site pruritus); headache (PT: headache); insomnia (PT: insomnia); nausea (PT: nausea); diarrhea (PT: diarrhea); and vomiting (PT: vomiting) (see ESM eTable 13).

A free-text option was provided to collect other adverse events not considered a priori in the predefined list. Reactions collected within the free-text option were considered unsolicited ARs.

Severe ARs were defined by intensity assessed on a Likert scale, with values ranging from 0 to 10, rated using instructions from the interviewer (see ESM eFig. 1).

2.3 Delivery of the Questionnaire

2.3.1 Preparatory Process

Nine professionals from the Medical Division were trained ad hoc and delivered the questionnaire through phone calls. A guiding document was drafted, which aimed to homogenize its administration. Simulations with ten dummy cases were performed to homogenize the delivery process amongst interviewers.

2.3.2 Implementation

Calls were made after each dose. At least three phone call attempts were made to each interviewee to maximize responsiveness. For HCPs, if we did not obtain a response on at least two separate calendar days, interviewees were then contacted at their institutional email addresses and asked whether: (i) They wanted to be further contacted by phone at a preferred phone number and timeslot; (ii) they preferred to be contacted and answer the questionnaire by email; (iii) they did not want to be contacted further. For interviewees who chose to answer the questionnaire by email, an electronic version was enabled, constructed using Lyme Survey technology (enquesta.clinic.cat).

During the implementation process, there were regular team meetings for doubt resolution and consistency of data recording.

2.4 Variables Assessed

The structure of the questionnaire was based on two blocks, which were completed after the first and second doses for all participants.

The first block contained common background variables that were completed by all participants (HCPs and SOTRs) and specific background variables for each vaccinated group. The second block contained vaccine- and AR-related variables, which were completed by all participants.

2.4.1 First Block

Common background variables: Age, sex, medical background; SARS-CoV-2 infection history (positive PCR or antigen test, positive serology, and/or symptomatic infection with or without hospital admission).

Specific background variables: For HCPs, contact with SARS-CoV-2 patients in their daily activity (yes/no) was included in this first block. In case of SOTRs, type of transplant (liver, heart, kidney, kidney-pancreas) was considered.

2.4.2 Second Block

Vaccine and AR related variables: Date of vaccination; type of vaccine administered; AR start date, end date (where available), reported AR, and intensity of AR. Types of ARs were selected from a predefined list in the questionnaire. The interviewer asked a closed-question to assess whether the participant had had the AR (e.g., "Did you have fever"?). The interviewer recorded yes or no. These ARs were considered "solicited ARs."

A free-text option called "other" was enabled to collect other ARs not considered a priori in the drop-down list. To explore "other ARs" the interviewer asked an open question (e.g., Have you had other types of AR?). Yes or no was recorded accordingly. If yes, the specific type of AR was recorded as a narrative description. These AR were considered "unsolicited ARs."

2.5 Data Collection and Data Management for Clinical Follow-Up

A database was designed and implemented with MACRO™, which provided electronic data capture functionality (EDC) to support electronic data entry. Data completion and integrity of the database were assessed continuously to verify the information consistency and completeness. Hospital electronic records were reviewed to capture potential reactions not collected by the structured interview and to mitigate recall bias.

Solicited and unsolicited ARs were coded using the PT and System Organ Class (SOC) categories of version 24.0 of MedDRA. There was considerable heterogeneity in the way unsolicited ARs were reported and recorded. Therefore, unsolicited ARs were grouped within the closest related SOC and PT.

2.6 Statistical Analysis

2.6.1 Sample Size Calculation

There was no formal sample size calculation. We included all vaccinated HCPs and SOTRs who did not decline taking part in the survey.

2.6.2 Planned Analyses and Assessed Variables

Three groups were considered for analysis: HCPs vaccinated with BNT162b2, HCPs vaccinated with mRNA-1273, and SOTRs vaccinated with mRNA-1273. Two main comparisons were planned within these three groups: (i) A comparative analysis of the vaccine tolerability and reactogenicity profile between vaccines in HCPs, after the first and second doses; (ii) a comparative analysis of the tolerability and reactogenicity of vaccination between HCPs and SOTRs vaccinated with mRNA-1273, after the first and second vaccine doses. Tolerability was assessed by a Likert scale ranging from 0 to 10. Reactogenicity was assessed by the proportion of ARs in each group.

The key secondary endpoint was to describe solicited and unsolicited ARs recorded in each group, according to reported frequencies and intensity distribution. Comparison of the risk of any severe AR (Likert scale score 7–10) in the three study groups was also considered as an exploratory endpoint.

2.6.3 Statistical Analysis

Categorical variables were described as frequencies and percentages and continuous variables as mean ± standard deviation or median (25–75% interquartile range), as appropriate. Categorical data were compared using the chi-square test and continuous variables using ANOVA with rank-transformed data. To assess baseline homogeneity, we used standardized differences (STDs, differences between groups divided by pooled standard deviation). To compare vaccination in HCPs, the inverse probability of the treatment weights (IPTWs) approach [28] was used to create a pseudo-population in which the two groups were balanced across baseline covariates. The stabilized weights were calculated using propensity scores (PS) [29] aimed to minimize the between-arm standardized differences [30]. Covariate balance was assessed using STDs to achieve absolute values < 0.20 ($|< 20\%|$), which are acceptable values of variability [31, 32]. Variables included in the IPTW construction were comorbidities; previous exposure to SAR-CoV-2; job position and SARS-CoV-2 occupational contact with patients; sex; age (per 1-year strata).

STDs were also calculated to compare HCPs and SOTRs and compare the three study groups. However, IPTW was not applied in the HCP and SOTR comparisons as they were very different populations and the key covariates inherent in each group were not modifiable, and the main outcome was to describe whether the same vaccine was tolerated differently in the two populations. The primary analysis of the comparison of the risk of ARs between vaccines in HCPs (BNT162b2 and mRNA-1273) after the first and second doses was based on IPTW methods. Sensitivity analyses were performed considering raw unadjusted data and covariate-adjusted data. Raw and adjusted regression models were used to estimate odds ratios (ORs) with 95% confidence intervals (CIs) for all model variables. The area under the curve of the receiver operating characteristics (AUC ROC) curve was calculated to assess model performance.

The primary analysis of the comparison of the risk of ARs between HCPs and SOTRs vaccinated with mRNA-1273 was based on covariate-adjusted data using only age, sex, previous SARS-CoV-2 infection, and a history of drug allergy. Adjusted regression models were used to estimate OR with 95% CI for all model variables. The AUC of the ROC curve was calculated to assess the performance of the model.

To analyze the key secondary endpoint, the rate of vaccinated persons with ≥ 1 AR was calculated for each vaccine and dose. The rate of each individual AR (solicited plus unsolicited) was calculated. Intensity was categorized, according to Likert scale values, as low grade or mild (grade 1; score 0–3), moderate grade (grade 2; score 4-6) and severe grade (grade 3; score 7-10). For each type of AR, the rate of vaccinated personnel with grade 3 ARs and median intensity was calculated.

In all analyses, we applied a two-sided type I error of 5%. SAS v9.4 (Cary, NC, USA) software was used throughout.

3 Results

3.1 Cohort Characteristics

Overall, 7907 HCPs were vaccinated with ≥ one vaccine dose. Of these, 6865 received two doses. Sixty four percent (5088) of HCPs participated in the survey and were included in the analysis. Of these, 3564 HCPs were vaccinated with BNT162b2 (of whom 2790 received the second dose), and 1524 were vaccinated with mRNA-1273 (of whom 1331 received the second dose). Likewise, 1806 SOTRs were vaccinated with two doses of mRNA-1273, of whom 77% (1289 patients) participated in the study. Of those, 1289 patients received one dose and 1132 received two doses.

Of the final population, a similar proportion of participants received the second dose in the three groups. There was a higher proportion of female participants amongst HCPs ($p \leq 0.001$, STD = 29), whereas the proportion was inverted in SOTRs, with a higher proportion of male vaccinated participants ($p \leq 0.001$, STD = 74). The mean age was comparable amongst HCPs (41.15 and 43.01 years; $p \leq 0.001$, STD = 14) but was higher in SOTRs (61.21 years; $p \leq 0.001$, STD = 137). Occupational SARS-CoV-2 contact was significantly higher in HCPs vaccinated with BNT162b2 compared with those vaccinated with mRNA-1273 ($p \leq 0.001$, STD = 29). Previous SARS-CoV-2 infection was higher in HCPs vaccinated with mRNA-1273 compared with those vaccinated with BNT162b2 and SOTRs ($p \leq 0.001$, STD = 21 and 35 for the comparisons between HCPs and SOTRs, respectively). SOTRs had a higher proportion of comorbidities, including drug allergies. Baseline characteristics of the population are shown in Table 1.

3.2 Adverse Reactions

3.2.1 Comparison Between Vaccines

In total 85.3% of the 5088 HCPs had ≥ one AR. The number of HCPs with any AR was 2878 (81.2%) after vaccination with BNT162b2 and 1463 (92.9%) after vaccination with mRNA-1273 (Table 2).

In the multivariate analysis, mRNA-1273 showed greater reactogenicity than BNT162b2, with an OR for any AR of 3.04 (95% CI 2.48–3.73; $p < 0.001$) in the main analysis adjusted by IPTW. Covariate-adjusted sensitivity analyses consistently showed significant results. Younger age, female sex, a history of drug allergies, and previous SARS-CoV-2 infection were significant in the covariate-adjusted model and increased the risk of ARs. Variables selected from the standard univariate model are shown in Table 3 with their respective ORs and 95% CIs. The ROC AUC curve had a value of 0.770 (95% CI 0.752–0.787). The exploratory multivariate analysis based on severe ARs showed similar results to the model constructed for any AR (see ESM eTable 12).

Comparing BNT162b2 with mRNA-1273, local ARs such as injection site pain (1228 (34.7%) vs. 838 (49.4%)), arm pain (941 (26.6%) vs. 665 (39.2%)), and systemic ARs such as fatigue (915 (25.9%) vs. 533 (31.4)), headache (850 (24.0%) vs. 547 (32.3%)), and fever (851 (24.0%) vs. 737 (43.5%)), were the most frequently reported solicited ARs for the two vaccines (see ESM eTable 2). Greater rates of injection site pain, fever, and arm pain were observed in the mRNA-1273 cohort than in the BNT162b2 cohort. Unsolicited AR rates were comparable between vaccines, except for hypersensitivity and lymphadenopathy, which were more frequent with mRNA-1273 (see ESM eTable 2, eFig. 2).

Mild (LS: 0-3) or moderate (LS: 3-6) ARs were reported in 66.3% of participants vaccinated with BNT162b2, and 43.6% of those vaccinated with mRNA-1273. Severe ARs (proportion of ARs with Likert scale score ≥ 7) were reported more frequently with mRNA-1273 than with BNT162b2 (56.4% vs. 33.7%, respectively). Severe systemic ARs were more frequent after the second dose: fatigue, headache, myalgia, malaise, arthralgia. No differences were observed after the second dose for severe local ARs. The mean and median Likert scale scores of ARs were higher with mRNA-1273. No significant differences were observed in the mean and median Likert scale scores between the different types of ARs nor between the first and second vaccine doses. Malaise was the AR with the highest mean and median Likert scale score in both groups (ESM eTables 3–6).

3.2.2 Comparison Between Healthcare Professionals (HCPs) and Solid-Organ Transplant Recipients (SOTRs)

SOTRs had fewer ARs than HCPs (1016 out of 1289 (78.8%) vs. 1463 out of 1524 (96%), respectively). A lower proportion of ARs was reported after the second dose in both groups (Table 4). In the covariate-adjusted multivariate analysis, the variable "population (SOTRs vs. HCPs)" was significant, with OR = 0.36 (95% CI 0.25–0.50). Younger age, previous SARS-CoV-2 infection, and female sex were significant and increased the risk of reactogenicity risk. A history of drug allergies was not a significant covariate in SOTRs in the covariate-adjusted multivariate analysis. Variables selected from the standard univariate model to build the multivariate model are shown in Table 5 with their respective ORs and 95% CIs. The ROC AUC curve had a value of 0.778 (0.752–0.805). The exploratory multivariate analysis considering severe ARs showed comparable results to the model constructed for any AR (see ESM eTable 12), except for drug allergies, which yielded significant results in SOTRs, unlike the main analysis with any AR.

Table 1 Baseline characteristics of participants: healthcare professionals (HCPs) and solid-organ transplant recipients (SOTRs)

	Population			Comparisons			
				HCP BNT162b2 vs. HCP mRNA-1273		HCP mRNA-1273 vs. SOTR mRNA-1273	
	HCP BNT162b2 (n = 3564) n (%)	HCP mRNA-1273 (n = 1524) n (%)	SOTR mRNA-1273 (n = 1289) n (%)	p value	STD (%)	p value	STD (%)
Number of doses							
1 dose	3564 (100)	1524 (100)	1289 (100)	–	0	–	0
2 doses	2790 (78.3)	1331 (87.3)	1132 (87.8)	< 0.001	24	0.698	1
Gender							
Male	1044 (29.3)	461 (30.2)	838 (65.0)				
Female	2520 (70.7)	1063 (69.8)	451 (35.0)	0.494	2	< 0.0001	74
Age (years)							
Mean (SD)	41.15 (12.60)	43.01 (14.20)	61.21 (12.29)				
Median (P25, P75)	41.00 (30.0, 52.0)	43.00 (30.0, 55.0)	62 (54.0, 70.0)	< 0.001	14	< 0.001	137
Age strata (n, %)							
18–30	974 (27.3)	395 (25.9)	23 (1.8)				
31–40	794 (22.3)	289 (19.0)	51 (4.0)				
41–50	806 (22.6)	316 (20.7)	164 (12.7)				
51–65	942 (26.4)	470 (30.8)	518 (40.2)				
> 65 years	48 (1.3)	54 (3.5)	533 (41.3)	< 0.0001	14	< 0.001	141
Occupational SARS-CoV-2 contact							
In contact with SARS-CoV-2 patients	1644 (46.1)	484 (31.8)	–	< 0.001	29	–	–
Without contact with SARS-CoV-2 patients	1915 (53.7)	1038 (68.1)	–	< 0.001	29	–	–
Previous SARS-CoV-2 infection[a]							
Yes	354 (9.9)	262 (17.2)	78 (6.1)				
No	3210 (90.1)	1262 (82.8)	1211 (93.9)	< 0.001	21	< 0.001	35
Comorbidities							
Any comorbidity[b]	1267 (35.5)	512 (33.6)	705 (54.7)	0.404	4	< 0.001	43
Hypertension	122 (3.4)	61 (4.0)	310 (24.0)	0.309	3	< 0.001	60
Diabetes mellitus	38 (1.1)	18 (1.2)	223 (17.3)	0.719	1	< 0.001	58
Heart failure	10 (0.3)	2 (0.1)	37 (2.9)	0.314	3	< 0.001	23
Chronic bronchitis	7 (0.2)	6 (0.4)	7 (0.5)	0.202	4	0.561	2
Asthma	126 (3.5)	46 (3.0)	11 (0.9)	0.350	3	< 0.001	16
Rheumatic/immune-mediated disease	33 (0.9)	12 (0.8)	9 (0.7)	0.629	2	0.784	1
Drug allergies	294 (8.2)	113 (7.4)	145 (11.2)	0.315	3	0.000	13
Food allergies	154 (4.3)	54 (3.5)	19 (1.5)	0.199	4	0.001	13

[a]Diagnosis by RCP, antigen test, and antibody positive serology

[b]Number of vaccinees with at least one comorbidity

A smaller proportion of solicited and unsolicited ARs was reported in the group of SOTRs, compared with HCPs. There were fewer systemic ARs, such as fever (202 (15.7%) vs. 774 (50.8%)), malaise (113 (8.8%) vs. 400 (26.2%)), chills (109 (8.5%) vs. 341 (22.4%)), fatigue (251 (19.5%) vs. 532 (34.9%), myalgia (62 (4.8%) vs. 337 (22.1%), arthralgia (39 (3.0%) vs. 203 (13.3%)), as well as a smaller proportion of some local and reactogenic reactions, such as injection site redness (28 (2.2%) vs. 145 (9.5%)), injection site pruritus (21 (1.6%) vs. 87 (5.7%)) and arm pain (345 (26.8%) vs.

Table 2 Main results of the comparison of BNT162b2 vs. mRNA-1273 in HCPs. Raw and IPTW analyses on proportions of any adverse reaction

Patients with ≥ 1 adverse reaction	BNT162b2 ($n = 3564$) n (%)	mRNA-1273 ($n = 1524$) n (%)
Raw analysis		
Overall	**2878 (80.8)**	**1463 (96.0)**
Reactions after first dose	2054 (57.6)	1252 (82.2)
Reactions after second dose	2161 (60.6)	1209 (79.3)
IPTW analysis		
Overall	**2873 (81.2)**	**1576 (92.9)**
Reactions after first dose	2038 (57.6)	1344 (79.2)
Reactions after second dose	2190 (61.9)	1229 (72.5)

Frequency of adverse reactions in both vaccinated groups of HCPs (BNT162b2 and mRNA-1273) and after each dose of vaccine; p value < 0.001 for all comparisons. Main results are displayed in bold

HCPs healthcare professionals, *IPTW* inverse probability of the treatment weights

624 (40.9%)). There was also a lower proportion of immune-mediated ARs, such as hypersensitivity or lymphadenopathy (see ESM eTable 7, eFig. 3).

Mild (Likert 0–3) or moderate (Likert 3–6) ARs were reported in 75.6% of SOTRs and 41.9% of HCPs vaccinated with mRNA-1273. Severe AR (Likert score ≥ 7) were reported more frequently in HCPs after vaccination with mRNA-1273 (58.1% vs, 24.4%, respectively). Severe systemic ARs (fatigue, headache, myalgia, malaise, arthralgia) were more frequent after the second dose in HCPs, but not in SOTRs. No significant differences were observed after the second dose for severe local ARs in either group. Mean and median Likert scores were lower for SOTRs, for the whole set of ARs and for each specific AR (ESM eTables 8-11). Arthralgia was the AR with the highest mean and median Likert score in both groups.

4 Discussion

The relevance of our study lies in the provision of additional real-world evidence on the safety profile of vaccination, in a prospective comparative study where two vaccines (BNT162b2 and mRNA-1273) and two populations (HCPs and SOTRs) vaccinated with mRNA-1273 were compared using the same structured questionnaire.

Randomized clinical trials of mRNA-based vaccines reported an overall acceptable safety profile [1, 2]. The higher rate observed for mRNA-1273 in our study (increase of 11.7% in the rate of any observed AR compared with BNT162b2 (92.9% vs. 81.2%)) is consistent with that reported for the pivotal mRNA-1273 study, and the profile of reported systemic and local ARs. However, while this higher rate for mRNA-1273 is consistent with reports from the respective clinical trials, the rate of any AR found for the two vaccines was substantially higher than that reported in clinical trials (81.2% vs. 27% and 92.9% vs. 87.8% for BNT162b2 and mRNA-1273, respectively). This may reflect differences in the adverse events reported between studies. For instance, data related to the pivotal clinical trial of BNT162b2 must be interpreted with caution, since the rate of any AR was calculated from the overall study population, whereas local and systemic ARs were collected from a "reactogenicity" subset of vaccinated persons. This is clearly a different way of reporting ARs in the pivotal Pfizer study. Despite these differences, our results are in line with safety information provided for BNT162b2 and mRNA-1273 in the respective Summaries of Product Characteristics [23, 26]

After the pivotal clinical trials, millions of doses of mRNA and other SARS-CoV-2 vaccines have been administered, including booster doses. Large-scale studies have been conducted, reporting that SARS-CoV-2 vaccines are safe [6, 33]. However, these studies are mainly based on electronic health records or adverse event reporting systems, and it is likely that mild or moderate symptoms are not systematically reported. Liu et al. analyzed 26 safety studies in a recent systematic review and meta-analysis of real-world studies of SARS-CoV-2 vaccines [34]. Sample sizes ranged from 77 to 2041 vaccinated persons. A large Japanese study of BNT162b2 assessed the safety of millions of vaccinated persons in Japan, although based only on spontaneous AR reporting [35]. Most of the 26 studies included were based on retrospective assessments of data or a single SARS-CoV-2 vaccine, and only a few small studies provided real-world comparative data. Most cases were based on retrospective assessment of data. Other studies with HCPs have been published, such as those by Riad et al. in HCPs in the Czech Republic and Slovakia [8, 9], with a similar sample size to the studies included in Liu´s revision (522 and 922 participants, respectively). A more recent Japanese study included 3254 HCPs vaccinated with BNT162b2 [11], and another recent Maltese study included 1480 HCPs vaccinated with BNT162b2 [36]. Another recent study, designed as a cohort event-monitoring study, included 22,184 participants vaccinated with BNT162b2, mRNA-1273, and other types of vaccines, such as Vaxzevria® [7]. Our results (in terms of proportions, severity, and types of reported AR) are in line with the results of these published studies.

Some prospective studies have specifically targeted safety in vaccinated SOTR. Cucchiari et al. found that patient-reported side effects on a semiquantitative scale (none/mild/moderate/severe) were consistent with the pivotal trial, and no donor-specific antibodies were detected [13]. Another prospective study in kidney transplant recipients (the RECOVAC-IR study) is ongoing [37]. Ou et al. studied

Table 3 Comparison 1: BNT162b2 vs. mRNA-1273 in HCPs. Risk of any adverse reaction (AR) estimated by inverse probability of the treatment weights (IPTW) and univariate and multivariate logistic regression models

Variables	Univariate model		Multivariate model[a]		IPTW model	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value
BNT162b2 (Ref: mRNA-1273)	**5.72 (4.37–7.48)**	**< 0.001**	**5.40 (4.08–7.13)**	**< 0.001**	**3.04 (2.48–3.73)**	**< 0.001**
Female sex	1.89 (1.61–2.22)	< 0.001	1.99 (1.68–2.37)	< 0.001	–	–
Age (risk change per 1 year younger)	1.02 (1.01–1.02)	< 0.001	1.02 (1.01–1.03)	< 0.001	–	–
Age strata (year)						
≤ 30	1 (Ref)	< 0.001	–	–	–	–
31–40	0.95 (0.74–1.21)		–	–	–	–
41–50	0.74 (0.59–0.94)		–	–	–	–
51–65	0.59 (0.48–0.73)		–	–	–	–
> 65	0.30 (0.19–0.47)		–	–	–	–
Previous SARS-CoV-2 occupational contact	1.05 (0.89–1.23)	0.573	–	–	–	–
Previous SARS-CoV-2 infection	1.95 (1.46–2.62)	< 0.001	1.77 (1.30–2.41)	< 0.001	–	–
Any previous comorbidity	1.31 (1.18–1.42)	< 0.001	–	–	–	–
Hypertension	0.87 (0.59–1.30)	0.505	–	–	–	–
Diabetes mellitus	1.03 (0.49–2.19)	0.934	–	–	–	–
Rheumatic/immune-mediated disease	0.93 (0.41–2.09)	0.865	–	–	–	–
Asthma	1.49 (0.91–2.44)	0.115	–	–	–	–
Heart failure	1.90 (0.24–14.70)	0.541	–	–	–	–
Chronic bronchitis	2.07 (0.27–15.93)	0.486	–	–	–	–
Previous drug allergies	1.46 (1.05–2.01)	0.022	1.57 (1.12–2.21)	0.010	–	–

Odds ratio (OR) (95% confidence interval (CI)) was used as the measure of the risk. Univariant and multivariant models were constructed as sensitivity analyses. The multivariate model was constructed using a forward stepwise selection approach of significant variables at univariate testing. Main results are displayed in bold

HCPs healthcare professionals

[a]ROC-AUC: 0.770 (0.752–0.787)

the safety and reactogenicity of BNT162b2 and mRNA-1273 in 741 SOTRs [38], and concluded that reactogenicity was similar to that reported in the original trials and severe reactions were rare. Overall, these previous safety data can help address vaccine hesitancy in SOTRs and other groups of immunocompromised patients. Nevertheless, further "real-world" data from prospective comparative studies in a "healthy population" are still needed to address in greater depth the comparative reactogenicity profile and thus consolidate this reassuring message. In a recent Israeli study, 80 liver transplant (LT) recipients and 25 controls were followed-up for 7–10 weeks after receiving the second dose of BNT162b2 [20]. Injection site reactions were reported at a similar frequency in both groups following the first and second doses. While the frequency of systemic events was similar in both groups after the first vaccination, they were significantly less frequent following the second dose among LT recipients. The most common systemic side effect was fatigue, followed by headache and myalgia. In our study, a decrease in the frequency and severity of ARs was already seen after the first dose, including injection site reactions.

Our study helps provide additional prospective comparative data on solicited and unsolicited ARs in a large sample size, thus providing robust comparative data from two vaccines and two populations of vaccinated persons with the same vaccine. In line with previous clinical trials and real-world studies, our results show a predominance of local, mild AR, which can be seen as a reassuring message of the safety of vaccination.

In addition, our data provide some evidence on the impact of relevant covariates, such as age, sex, and previous SARS-CoV-2 infection, showing a consistent effect independently of the scenario studied. In HCPs, mRNA-1273 showed a higher rate of any observed AR compared with BNT162b2. The severity of AR (Likert score ≥ 3) was also higher for mRNA-1273. Lower age, female sex, previous SARS-CoV-2 infection, and a history of drug allergies were significant independent covariates associated with the risk

Table 4 Main results of the comparison of solid-organ transplant recipients (SOTRs) and healthcare professionals (HCPs). Proportions of any adverse reaction

Patients with ≥ 1 adverse reaction	SOTRs (n = 1289) n (%)	HCPs (n = 1524) n (%)
Raw analysis[a]		
Overall	**1016 (78.8)**	**1463 (96.0)**
Reactions after first dose	875 (67.9)	1252 (82.2)
Reactions after second dose	699 (54.2)	1209 (79.3)

Frequency of ARs in SOTRs and HCPs (both vaccinated with mRNA-1273) and after each dose of vaccine. Main results are displayed in bold

[a]No IPTW or adjustment analyses were conducted since key covariates were inherent to any or other group and were not modifiable characteristics; p value < 0.001 for all comparisons

IPTW inverse probability of the treatment weights

of ARs, consistent with earlier reports [39–43]. The ROC AUC showed the acceptable performance of the multivariate model.

Comparison between HCPs and SOTRs (all vaccinated with mRNA-1273) showed a lower proportion and lower intensity of ARs in the latter group. This trend was consistent in the covariate-adjusted multivariate analysis. Age, sex, previous exposure to SARS-CoV-2, and belonging to the group of SOTRs showed a significant impact in the development of ARs. Previous history of drug allergies, which was a significant covariate in the covariate-adjusted analysis of HCP, was only significant in SOTRs when severe ARs were considered. These findings strongly support the idea that immunosuppressive therapy—and reduced immunogenicity—can play a role in the short-term tolerability of mRNA SARS-CoV-2 vaccines.

Less clear is the influence of sex on the tolerability of vaccination in healthy persons and SOTRs. Pivotal clinical trials did not specifically address potential sex-related differences. We observed more ARs in vaccinated females. Indeed, sex-based differences do not seem to be circumscribed to vaccines, but rather seem a general pattern also shown by other types of medicinal products [44, 45]. Sex-based immunological differences have been hypothesized and our data could at least partially support this [46, 47]. However, other underlying mechanisms such as pharmocokinetcs/pharmacodynamics, and social and behavioral causes still require further elucidation.

In sum, the results of this study show an increased reactogenicity of mRNA-1273 in terms of a higher proportion

Table 5 Comparison 2: solid-organ transplant recipients (SOTRs) vs. healthcare professionals (HCPs) (vaccinated with mRNA-1273). Risk of any adverse reaction (AR) estimated by univariate and multivariate logistic regression models

Variables	Univariate model		Multivariate model[a]	
	OR (95% CI)	p value	OR (95% CI)	p value
Population (SOTRs vs. HCPs)	0.16 (0.12–0.21)	< 0.001	0.36 (0.25–0.50)	< 0.001
Sex	2.83 (2.22–3.61)	< 0.001	1.55 (1.19–2.02)	0.001
Age (risk change per 1 year younger)	1.06 (1.05–1.08)	< 0.001	1.04 (1.03–1.05)	< 0.001
Age strata (year)				
≤ 30	1 (Ref)	< 0.001		
31–40	1.09 (0.45–2.61)		–	–
41–50	0.40 (0.20–0.79)		–	–
51–65	0.25 (0.13–0.45)		–	–
> 65	0.07 (0.04–0.13)		–	–
Previous SARS-CoV-2 infection	2.99 (1.78–5.00)	< 0.001	2.09 (1.22–3.60)	0.008
Any previous comorbidity	1.05 (0.80–1.25)	0.667	–	–
Hypertension	0.69 (0.51–0.93)	0.017	–	–
Diabetes mellitus	0.75 (0.51–1.08)	0.125	–	–
Rheumatic/immune-mediated disease	2.71 (0.36–20.22)	0.332	–	–
Asthma	1.41 (0.56–3.55)	0.468	–	–
Heart failure	0.30 (0.15–0.59)	< 0.001	–	–
Chronic bronchitis	0.74 (0.16–3.35)	0.696	–	–
Previous drug allergies	3.20 (1.00–10.21)	0.049	1.42 (0.91–2.21)	0.120

The risk of ARs in the main comparison between vaccines was calculated. Odds ratio (OR) (95% confidence interval (CI)) was used as the measure of the risk. Univariant and multivariant models were constructed as sensitivity analyses. The multivariate model was constructed using a forward stepwise selection approach of significant variables at univariate testing

[a]ROC-AUC: 0.778 (0.752–0.805)

of ARs, but with an adequate tolerability profile of the two mRNA vaccines substantiated by the high number of mild and moderate ARs. A better reactogenicity and tolerability profile of mRNA-1273 was observed in SOTRs, in terms of a lower proportion of ARs and a lower proportion of severe ARs.

Our study had limitations linked to the observational and non-randomized nature, such as recall bias and potential confounders that may persist after the application of balancing and adjustment methods. In addition, vaccinated participants who agreed to participate may not be fully representative of the general population (e.g., participants who engage may be more prone to report ARs). The study was designed to capture short-term ARs and, due to its sample size, was not powered to detect rare ARs. In addition, severity (according to CIOMS (Council for International Organizations of Medical Sciences) criteria) was not assessed. Considering the results of clinical trials, which provided the core reference safety information when the study was designed, major complications or major reactions leading to hospital/emergency room admission or death within a short timeframe were in principle not expected. Therefore, severity was not collected in the questionnaire.

5 Conclusions

Our analysis supports existing evidence that mRNA-1273 has greater short-term reactogenicity than BNT162b2. However, most observed ARs were local and mild in intensity, confirming the tolerable safety profile of the two vaccines. These results may be interpreted as a reassuring message for the medical and scientific community, even if vaccinated participants who agreed to participate may not be fully representative of the general population.

Data suggest a link between increased reactogenicity and greater immunogenicity, as suggested by the fact that younger age and previous exposure to SARS-CoV-2 were consistently associated with an increased incidence of ARs, while a reduced immune status was linked to reduced vaccine reactogenicity and better tolerability. The effect of sex must be further examined. The correlation of reported ARs and immunologic parameters could provide further insight into the role of immunogenicity. This is a question our group is currently trying to answer in a second project.

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Declarations

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Conflict of interest None of the authors have any conflicts of interest to disclose.

Availability of data and material No data are available.

Ethical approval All procedures performed in studies involving human participants were carried out in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Research Ethics Committee of the Hospital Clinic (HCB/2021/0684 and HCB/2021/0685).

Consent A waiver of informed consent was approved for the project, since the surveillance program was considered part of normal medical care activity in the context of an innovative therapeutic strategy never tested before. However, an information leaflet on the program was made available to all vaccinated subjects. Participation in the surveillance was voluntary.

Author contributions The corresponding author (JSP) states that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. Joaquín Sáez-Peñataro (JSP), Gonzalo Calvo (GC), and Ferran Torres (FT) had full access to all of the data

in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: JSP, GC, FT, and Joan Bartra (JB). Acquisition, analysis, or interpretation of data: JSP, GC, FT, JB, Juan Bascuas (JBA), Anna Vilella (AV), Marta Tortajada (MT), Sebastiana Quesada (SQ), Elisenda González (EG), Ester López-Suñé (ELS), Antoni Castells (AC), Sandra Serrano (SS), Concepción Camacho (CC), and Antoni Trilla (AT). Drafting of the manuscript: JSP, GC, FT, and JBA. Critical revision of the manuscript for important intellectual content: JSP, GC, FT, JB, JBA, AV, MT, SQ, EG, ELS, AC, SS, CC, and AT. Statistical analysis: FT. Data management and EDC: SS. The lead author (JSP) confirms that the article is an honest, accurate, and transparent account of the study being reported and there are no important aspects of the study that have been omitted or any discrepancies from the study as planned have been reported and explained.

Code availability Not applicable.

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